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II. REMARKS

Claims 1-12 and 44-55 are presently pending in this application. All claims stand rejected under 35 U.S.C. §112, first paragraph. These rejections are believed to be overcome by the above amendments and are otherwise traversed for reasons discussed below.

Statement of Substance of the Interview

Applicants thank the Examiner for the telephonic interview of July 15, 2003 and for the helpful suggestions provided therein. The Examiner suggested that applicants incorporate language regarding conservative substitutions into the claims in order to obtain sequence variation. Applicants have so done.

Overview of the Above Amendments

Claims 1 and 4 have been amended to claim the subject invention with greater particularity. Specifically, as discussed with the Examiner, claims 1 and 4 now recite that any variation in the claimed molecule is due to conservative amino acid substitutions. Support for this recitation can be found throughout the application at, e.g., page 10, lines 9-27.

Rejection Under 35 U.S.C. § 112, First Paragraph

All claims stand rejected under 35 U.S.C. § 112, first paragraph as nonenabled. The Office acknowledges the specification enables an isolated nucleic acid molecule that encodes the amino acid sequence of SEQ ID NO:2. However, the Office argues the application "does not reasonably provide enablement for an isolated nucleic acid molecule encoding a polypeptide having at least 90% sequence identity to SEQ ID NO:2 or 5." Office Action, page 2. In support of this statement, the Office asserts:

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> The art teaches that replacement of a single amino acid residue may lead to both structural and functional changes in the biological activity of a protein. One of skill in the art would be reduced to merely randomly altering amino acids that would lead to unpredictable results regarding the functional activity of the immunogenic polypeptide...Applicants have not taught which residues of SEQ ID NO:2 or 5 that can be varied by 10% and still achieve the desired polypeptide. The skilled artisan would have to discover what the appropriate additions, deletion and substitutions could be.

Office Action, page 3. However, applicants submit that the claims are indeed enabled.

The invention is directed to nucleic acid molecules which encode specified "immunogenic" polypeptides. As explained to the previous Examiner, these nucleic acid molecules need not encode a CAMP factor with "biological activity" i.e., one displaying CAMP cytolytic activity. Indeed, such cytolytic activity is toxic and undesirable. Thus, the Office's concern with preserving the biological activity of the CAMP factor is in error. Rather, applicants' are providing nucleic acid molecules that encode immunogenic (e.g., epitope-containing) CAMP factor polypeptides.

Moreover, the immunogenic polypeptides need not retain their native conformation. Rather, epitopes contained within the immunogenic polypeptides need not be conformational, as evidenced by the fact that the CAMP factor polypeptide used in the examples does not retain its native conformation since it has been denatured and no refolding step is employed prior to use. Therefore, the Office's concern with "structural" changes specified above is also in error.

Applicants submit that one of skill in the art would not find it unduly burdensome to identify immunogenic polypeptides containing linear epitopes. Techniques for doing so are discussed in the patent application at page 13, lines 10-20. Applicants explain therein that immunogenic CAMP factor polypeptides can be rapidly and readily identified using, e.g., techniques described in issued U.S. Patent No. 4,708,871. The method detailed in the '871 patent involves concurrently synthesizing large numbers of peptides on solid supports, the peptides corresponding to portions of the protein molecule, and reacting the peptides with antibodies while the peptides are still attached to the supports. These methods can easily be used to identify immunogenic polypeptides derived from the

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S. uberis CAMP factor protein without undue experimentation. The Office is reminded that even a large amount of experimentation is permitted under §112, first paragraph, provided it is routine. *Ex parte Jackson*, 217 USPQ 804, 807 (Bd. App. 1982) (a claim is acceptable under §112 even if it requires extensive experimentation, as long as the experimentation is routine).

Furthermore, 35 U.S.C. §112, first paragraph does not require that specific examples be present in order to satisfy the enablement requirement. In fact, how an enabling teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance since a specification which teaches how to make and use the invention in terms which correspond in scope to the claims must be taken as complying with the first paragraph of §112 unless there is reason to doubt the objective truth of the statements relied upon therein for enabling support (*In re Marzocchi*, 169 USPQ 367 (CCPA 1971)).

Additionally, there is no requirement that applicants present data pertaining to each and every embodiment covered in a broad claim. Indeed, the CCPA in *In re Angstadt*, 190 USPQ 214 (CCPA 1976), cautions against such a burdensome requirement:

> Appellants have apparently not disclosed every catalyst which will work; they have apparently not disclosed every catalyst which will not work. The question, then, is whether in an unpredictable art, section 112 requires disclosure of a test with every species covered by a claim. To require such a complete disclosure would apparently necessitate a patent application or applications with 'thousands' of examples or the disclosure of 'thousands' of catalysts....More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed. A potential infringer could readily avoid 'literal' infringement of such claims by merely finding another analogous catalyst complex which could be used in 'forming hydroperoxides'. (Emphasis in original.)

Id. at 218.

Applicants submit that they have indeed complied with the enablement requirement of 35 U.S.C. §112, first paragraph. Routine methods for mapping epitopes

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were known to those of skill in the art at the time the application was filed and are taught in the specification. Given the level of skill in the art, the description in the specification and the particular examples, a skilled artisan could readily practice the claimed invention without undue experimentation. Applicants have therefore met their duty under 35 U.S.C. §112, first paragraph and respectfully request withdrawal of this rejection.

Nevertheless, in an effort to advance prosecution, applicants have amended independent claims 1 and 4 as suggested by the Examiner, to specify that any variation between the claimed immunogenic polypeptide and the specified amino acid sequence is due to conservative amino acid substitutions. Claims 2, 3 and 5-12 either directly or ultimately depend from clams 1 or 4. Remaining claims 44-55 nowhere even recite percent identity and should not be subject to this rejection. Accordingly, withdrawal of this basis for rejection is respectfully requested.

The Office also argues:

> The specification does not provide a clear protocol by which the polypeptide comprising SEQ ID NO:5 or variants were isolated at the time the invention was made. The specification does not provide structural characterization of the complete open reading frame of the bacterial membrane, i.e., including a start codon...Absent characterization of the start codon, the genus of the polypeptides comprised of SEQ ID NO:5 or immunological variants is highly diverse and variant.

Office Action, page 4. However, applicants submit that the sequence of SEQ ID NO:5, as well as a sequence having conservative amino acid substitutions thereof, is indeed enabled.

As explained to the previous Examiner, amino acids 1-228 of SEQ ID NO:5 correspond to amino acids 29-256 of SEQ ID NO:2, namely, this sequence defines the mature molecule of SEQ ID NO:2, lacking the signal sequence. See, page 18, lines 20-28 of the application. It is well known that a mature protein sequence is produced by cleavage of the signal sequence from the precursor polypeptide. One of skill in the art would readily know that the mature protein could be expressed using the homologous signal sequence, a heterologous signal sequence, without a signal sequence at all, or as a fusion protein. If desired, a triplet encoding methionine could be added to the 5'-end of

the polynucleotide if necessary. Such techniques were highly routine in 1995, the priority date of the present application. In fact, a sequence which encodes amino acids 1-256 of SEQ ID NO:2 inherently encodes the protein represented by amino acids 1-228 of SEQ ID NO:5 as this is the resulting product of the precursor polypeptide when it is expressed in an appropriate host cell.

Accordingly, applicants submit that the claims reciting SEQ ID NO:5 are also enabled and withdrawal of this basis for rejection is respectfully requested.

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III. CONCLUSION

Applicants respectfully submit that the claims comply with the requirements of 35 U.S.C. §112. Accordingly, allowance is believed to be in order and an early notification to that effect would be appreciated.

If the Examiner notes any further matters which she believes may be expedited by a telephone interview, she is requested to contact the undersigned attorney at (650) 493-3400.

Respectfully submitted,

Date: 7/15/03

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